REMARKS

Claims 79-96 are pending in this case. Claims 79-81, 84-90 and 93-96 have been amended hereinabove. The amendments to these claims do not involve new matter.

FORMAL MATTERS AND THE REJECTIONS UNDER 35 U.S.C. 112, SECOND PARAGRAPH

In response to the Examiner comments in item 4 of the Office Action dated May 13, 1997, applicants have amended the first line of the specification to update the status of priority documents.

In response to the Examiner comments in item 5 of the Office Action dated May 13, 1997, applicants have amended the title so as to clearly indicate the claimed invention.

In response to the Examiner comments in item 6 of the Office Action dated May 13, 1997, applicants will submit the appropriate drawings and amend the Brief Description of the Drawings in accordance with these changes.

In response to the Examiner comments in item 7 of the Office Action dated May 13, 1997, applicants have amended the specification to include the designation "TM" where trademarks appear and have included the appropriate generic terminology after these designations.

Applicants respectfully traverse the Examiner's rejection articulated in item 9 of the Office Action dated May 13, 1997 because the specification does provide support for inhibiting T cell activation (see specification at page 48, beginning at line 1). While this rejection is traversed, in order to

further prosecution, applicants have amended claims 88-96 and replaced the term "activation" with "responses".

In response to the Examiner comments in item 11 of the Office Action dated May 13, 1997, applicants direct the Examiner to item 53 of the Office Action dated December 4, 1992 (paper #12). At item 53 in this Office action, the Examiner acknowledges that applicants' response dated August 24, 1992 and the communication dated September 11, 1992 satisfy the deposit requirement.

In response to the Examiner comments in item 13A of the Office Action dated May 13, 1997, applicants have amended claims 87 and 94 to clarify the fusion proteins covered by these claims. In response to the Examiner comments in item 13B of the Office Action dated May 13, 1997, applicants have amended the claims to clarify the subject matter by removing the terms "receptor" and "antigen".

In response to the Examiner comments in item 14 of the Office Action dated May 13, 1997, applicants reiterate that a terminal disclaimer will be provided in response to the double patenting rejections made in sections 23-26 of Paper No. 39.

REJECTIONS UNDER 35 USC §112, FIRST PARAGRAPH

At item 10 the Office Action dated May 13, 1997, the Examiner objected to the specification and rejected claims 79-96 for allegedly failing to provide an enabling disclosure due to the high degree of unpredictability in pharmaceutical therapies, the limitations of in vitro immune assays and the alleged insufficiency of the applicants' disclosure pertaining to in vivo use. In this rejection, the Examiner states "[t]he specification does not teach how to extrapolate data obtained from the

disclosed in vitro assays based upon B7Ig or CD28Ig or from other CD28-B7 inhibitors such as antibodies or CTLA-4 Ig to the development of effective in vivo human therapeutic methods, commensurate in scope with the claimed invention" (Office Action at item 10, page 4).

Applicants respectfully traverse the Examiner's rejections and note that rejections based on the enablement of B7 and CD28 immunoglobulin fusion proteins have been raised and withdrawn. Specifically, in Office Actions dated August 17, 1994, April 26, 1995 and December 27, 1995, the Patent Office rejected the claimed methods of regulating cellular processes mediated by B7 and CD28 fusion proteins on exactly the same grounds as the current rejection (Paper #29, pages 2-4; Paper #30, pages 2-6; Paper #36, pages 2-4, respectively). In response to these Office Actions, applicants presented arguments which overcome these rejections. As evidenced in the Office Action dated September 13, 1996, the Patent Office acknowledges that the specification is in fact "enabling for the use of B7Ig or CD28Ig in a method of inhibiting T cell proliferation" (Paper #39, item 21, page 2). Therefore, the current rejections to the B7Ig and CD28Ig fusion proteins in the context of enablement are improper.

The MPEP at 706.04 highlights the fact that the rejection of previously allowed claims is to occur only under certain defined circumstances. Specifically, such action is only appropriate when the Examiner uncovers new prior art. Moreover, full faith and credit is to be given to the action of a previous examiner unless their is a clear error in the previous action. This section of the MPEP further notes that a claim noted as allowable shall thereafter be rejected only after the rejection has been submitted to the primary examiner for consideration all facts and approval of the proposed action.

As the Patent Office acknowledges the specification's enablement of claims directed to CD28Ig and B7Ig fusion proteins, applicants respectfully point out that the only issues that remain are those related to the enablement of methods utilizing generic B7 or CD28 derivatives.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST AND SECOND PARAGRAPHS

At item 12 of the Office Action dated May 13, 1997, the Examiner asserts that the present claims are indefinite in the recitation of "B7" and "containing amino acid residues from about position 1 to about position 215 of the amino acid sequence corresponding to the extracellular domain of B7 antigen" because their characteristics are allegedly ambiguous and not defined. The Examiner further asserts that while the specification is enabled for a B7 protein as sequenced by Freedman et al., it does not reasonably provide enablement for any B7 protein.

In response, applicants traverse and note that the specification particularly points out the defining characteristic of B7, namely that it is the B cell ligand for CD28 (specification at page 43, beginning at line 13). The specification's disclosure of B7's role as the B cell ligand for CD28 serves to particularly point out the defining characteristic of this protein as claimed. In addition, applicants note that B7 is the single art accepted term for this molecule as first described by Freeman et al., in "B7, A NEW MEMBER OF THE Ig SUPERFAMILY WITH UNIQUE EXPRESSION ON ACTIVATED AND NEOPLASTIC B CELLS" *J. Immunol.* 143: 2741-2722 (1989). Further, art searches in this field (such as the one conducted by the Patent Office for paper # 9) establish that "B7" is understood by those skilled in the art to be the protein having the characteristics of the protein as claimed. Therefore, as "B7" clearly recites the claimed subject matter, the Examiner's rejection should be withdrawn.

As to the Examiner's assertion that the disclosure of a single B7 molecule does not provide enablement for any B7 protein, applicants respectfully traverse and note that the law is clear that applicants are not required to disclose every specie encompassed by the claims even in an unpredictable art.[1] Moreover, despite the fact that applicants do not disclose every known B7 molecule, the identification of other species in the class would not entail undue experimentation because applicants' disclosure outlines a number of different assays for the identification of B7 molecules as claimed.

The legal standard for establishing compliance with the requirements of Section 112, first paragraph is clear, namely, whether applicants have taught how to make and use the invention without undue experimentation. In the context of the rejection, there is no undue experimentation involved with determining which members of a class of B7 binding molecules will work in the claimed method.

There is no undue experimentation in identifying B7 molecules useful in the claimed methods because the specification guides one having ordinary skill in the art on how to determine which species among the B7 molecules are among those encompassed by claimed methods. Specifically, this is effected by the specification's disclosure of complementary and redundant assays for B7 molecules encompassed by the claims, i.e. those molecules which effect cellular processes in their capacity to act as the ligand for the CD28 molecule on T cells.

Applicants' disclosure teaches methods for regulating an immune response by specifically targeting the binding interactions of two well defined molecules, B7 and CD28. The claimed methods are narrowly focused to immunoregulation through these interactions and the disclosure

[1] *In re Angstadt and Griffin*, 190 USPQ 215, 218 (CCPA 1976).

provides examples of exemplary molecules as well as different assays which evaluate the utility of these molecules in the claimed methods.

The disclosed representative molecules and example assays allow the skilled artisan to evaluate any novel molecule for its ability to effect immune responses associated with B7 and CD28 binding interactions. In particular, any B7 molecule may be independently assayed via the multiple disclosed complementary tests for its ability to act as the ligand for CD28. In this way, the disclosure allows the skilled artisan, without undue experimentation, to determine which species among the claimed genus possesses the disclosed utility. The multiple complementary and redundant assays for molecules possessing the claimed utility are reviewed below.

In the specification at page 43, applicants disclose a protocol for a binding assays utilizing B7 and CD28 transfected COS cells to measure CD28 mediated adhesion. In this binding assay, the applicants disclose a method which evaluates the ability of COS transfected CD28 cells to bind COS cells transfected with a B7 molecule. As a control in these assays, applicants disclose both a B7 construct and an anti-CD28 monoclonal antibody 9.3 which specifically blocks this interaction. With this assay, any potential B7 molecule can be transfected into COS cells and tested for its ability to interact with CD28. As transfection constructs antibody blocking assays are well known in the art and the specification discloses representative constructs, these protocols are readily adapted for use in assays of a wide variety of molecules that have the potential to bind CD28.

In the specification at page 61, applicants disclose a protocol for an ELISA assay tailored to test B7 molecules' ability to bind CD28. This highly detailed description outlines the specific conditions for binding B7 molecules to immobilized CD28 molecules. As both B7 and CD28 constructs and ELISA protocols are well known in the art, the applicants' illustrative binding protocols may be used to assay a wide variety of molecules that may bind CD28. In addition, the

applicant's disclosure of the B7Ig construct provides a competitor with known binding characteristics to use as a control in these assays.

In the specification at page 66, applicants disclose a protocol for specifically measuring the effects of B7 binding on T cell proliferation. Specifically, a procedure for measuring T cell stimulation through CD28 is disclosed wherein T cell proliferation by B7 molecules is measured by uptake of [^{3}H] for 5 hours. As a control in these assays, applicants disclose both a B7 construct for use a control in evaluating other members of this class. This tritium uptake protocol utilized by applicants is well known in the art and the applicant's disclosure of such representative examples in the context of these proliferation protocols allow for ready adaptation of these protocols for use in assays of a wide variety of B7 molecules that have the potential to activate T cells through the CD28 molecule on the surface of T cells.

In addition to the specific binding protocols discussed above, applicant's disclosure of the specific B7 and CD28 constructs for use in such assay readily allows one skilled in the art to use other well known binding assays to evaluate a wide variety of molecules that may have the potential to bind CD28. In particular, the CD28 and B7 constructs and the disclosed antibodies to each may be used in co-immunoprecipitation assays. In such assays, any molecule that binds to CD28 will be copurified in an immunoprecipitation reaction due to its affinity for the target molecule. Such coimmunoprecipitation assays are well known in the art and are a standard procedure for identifying whether a novel molecule binds to a defined target. See Dedhar et al. which will be filed shortly as Exhibit 1.

The legal standard for enablement requires that there must be sufficient disclosure through illustrative examples or terminology to teach those of ordinary skill how to make and use the

invention as broadly as it is claimed.[2] This means that the disclosure "must adequately guide the art worker to determine, without undue experimentation, which species among the claimed genus possess the disclosed utility."[3] As discussed *infra* in the review of the specification's disclosed protocols, by providing illustrative examples and assays, applicants meet the standard for objective enablement of any B7 protein.[4]

No other fee or extension of time is deemed necessary in connection with the filing of this response. If any fee or extension of time is necessary, the Patent Office is authorized to effect a further extension of time and to charge any additional fee to Deposit Account No. 13-2724.

Respectfully submitted,

Sarah B. Adriano

I hereby certify that this paper is transmitted *via facsimile* to the U.S. Patent Office at (703) 308-4242.

Joe Gonzales 9.15.97
Signature Date

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[2] *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).
[3] *Id.*
[4] The first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). How such a teaching is set forth, either by the use of illustrative examples or by broad terminology is irrelevant. *Id.*